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Secular changes in functional disability, pain, fatigue and mental well-being in early rheumatoid arthritis. A longitudinal meta-analysis.

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Abstract

Objectives: To conduct a systematic review and longitudinal meta-analysis of early rheumatoid arthritis (RA) cohorts with long-term data on pain, fatigue or mental well-being.
Methods: Searches using PUBMED, EMBASE and PyscInfo were performed to identify all early RA cohorts with longitudinal measures of pain, fatigue or mental well-being, along with clinical measures. Using longitudinal meta-analyses, the progression of each outcome over the first 60-months was estimated. Cohorts were stratified based on the median recruitment year to investigate secular trends in disease progression.
Results: Of 7,319 papers identified, 75 met the inclusion criteria and 46 cohorts from 41 publications provided sufficient data on 18,046 patients for meta-analysis. The Disease Activity Scores (DAS28) and the Short-Form 36 (SF-36) Physical Component Score (PCS) indicated that post-2002 cohorts had statistically significant improvements over the first 60-months compared to pre-2002 cohorts, with standardised mean differences (SMD) of 0.86 (95% Confidence Intervals 0.34 to 1.37) and 0.76 (95% CI 0.25 to 1.27) respectively at month-60. However, post-2002 cohorts indicated statistically non-significant improvements in pain, fatigue, functional disability and SF-36 Mental Component Score (MCS) compared to pre-2002 cohorts, with SMD of 0.24 (95% CI -0.25 to 0.74), 0.38 (95% CI -0.11 to 0.88), 0.34 (95% CI -0.15-0.84) and -0.08 (95% CI -0.41 to 0.58) at month-60 respectively.
Conclusions: Recent cohorts indicate improved levels of disease activity and physical quality of life, however this has not translated into similar improvements in levels of pain, fatigue and functional disability by 60-months.

Keywords

Rheumatoid Arthritis, Systematic Review, Meta-Analysis, Cohort Studies

Introduction

Rheumatoid arthritis (RA) is a chronic auto-immune disease that causes inflammation and pain in joints. It is estimated to affect approximately 1% of the UK adult population[1]. Inadequately treated, it can lead to long-term physical damage, namely in the form of bone erosions and joint space narrowing, as well as reduced quality of life. The adoption of biologic Disease Modifying Anti-Rheumatic Drugs (bDMARDs) in the most severe cases[2], as well as the introduction of the Treat-2-Target (T2T) approach to disease management in the early 2000's[3], which employs the use of early, more aggressive conventional DMARD (csDMARD) therapies[4] have had a large impact on reducing inflammation and radiographic joint damage in recent years[5–7]. Despite this, there is little indication that this has translated into equivalently large, clinically-meaningful improvements in pain, fatigue and health related quality of life (HRQoL)[8–11]. This is of particular importance in RA populations, as there is evidence that patients with RA have higher prevalence of psychological distress, such as depression and anxiety[12–15] compared to the general population and that those patients with persistent depression have been evidenced to respond less well to bDMARD therapies[16]. Also, patients with RA with worse quality of life outcomes are associated with higher Health Care Resource Utilisation (HCRU)[17].

There is a sparsity of systematic reviews, including meta-analysis of quantitative data, investigating HRQoL outcomes. Matcham et al.[14] is one of the few published systematic reviews to investigate HRQoL in observational trials of RA populations, and demonstrated that HRQoL was lower in patients with RA when compared to other chronic conditions, such as Type 2 diabetes and congestive heart failure. However, much of the data presented were cross-sectional in nature, and as such does not document how HRQoL progresses over time, or indeed how modern approaches to treatment and management may have impacted on disease progression over different periods. To our knowledge, only one other review explored HRQoL in older patients with RA (≥75 years) and found that pain, increased age and increased functional disability all contributed to worse HRQoL[18].

The aim of this systematic review was to examine symptom severity and HRQoL at different points during the RA disease course and assess whether there have been changes in symptom levels and HRQoL over the last 30 years, in light of the substantial changes in treatment strategies over the last few decades.

Methods

Identifying publications

A systematic search of 3 databases, namely PubMed, EMBASE and PsycInfo, was conducted between 1975-2017. The search strategy used key words and MeSH terms on the title/abstract and full text as appropriate (See supplementary material for search terms used). Additional lateral search techniques included checking reference lists, performing key word searches in Google Scholar and using the 'cited by' option in PubMed. The review included all studies of adult patients (>18 years old) with early RA, where baseline assessment was <3 years from symptom onset. Diagnosis was confirmed by either the 1987 or 2010 American College of Rheumatology (ACR) criteria. As a systematic review of non-randomised observational cohorts, there was no intervention or comparator group of interest in this review.

Outcome(s)

The outcomes of interest were pain, fatigue and mental wellbeing. Pain and fatigue are typically measured using a Visual Analogue Scale (VAS), however other measures were eligible to be included. Mental health included any measures of quality of life, such as the EuroQol 5-Dimensions (EQ-5D) or the Short-Form 36 (SF-36). Other measures relating to depression and anxiety were also recorded if reported (e.g. Hospital Anxiety and Depression Scores (HADS) and the Beck Depression Inventory (BDI)).

Secondary outcome measures included clinical measures of disease, namely the Disease Activity Score (DAS) and measures of functional disability, namely the Health Assessment Questionnaire (HAQ).

Inclusion/exclusion criteria

Inclusion criteria to select publications comprised of: (1) included a measure of self-reported pain, fatigue or mental well-being, (2) patients had a diagnosis of rheumatoid arthritis, (3) baseline assessments occurred no later than 3-years from symptom onset, (4) prospective cohort study design, (5) had repeated measures (at least two time points), (6) included human participants, and (7) publications written in English.

Publication screening

One reviewer (RB) screened titles/abstracts identified in searches, using the selection criteria to identify potentially relevant papers. A second reviewer (LC) independently screened the title/abstract of 25% of all publications identified against agreed inclusion criteria. Agreement at the title/abstract stage was achieved in 92% of papers, with disagreements resolved through discussion (e.g. longitudinal data was only available for a subset of patients with established disease, not early disease). Both reviewers (LC & RB) then screened all full texts to establish the final set of studies to include in the review. Of the 1,736 full texts screened, agreement was achieved for 99.7% of papers.

Data extraction

Three reviewers (LC, RB and PM) extracted data using a pre-designed form, piloted to ensure all data necessary were captured. It included: cohort name, country of study population, pain/fatigue/mental well-being mean scores and Standard Deviation (SD), along with the outcome measure(s) used, number of patients included, years of recruitment, length of follow-up, proportion of females in the cohort, mean age of patients in the cohort, functional disability mean scores and SD at each recorded follow-up, Disease Activity Score mean and SD at each recorded follow-up (where this was recorded using the DAS44 method, a conversion formula was applied to convert it to DAS28[19]), proportion of patients in the cohort on DMARDS at baseline, proportion of patients in the cohort who were Rheumatoid Factor (RF) positive at baseline and number of patients at each follow-up. In cases where the raw data were not given in the published paper the author(s) were individually contacted to provide this data (n=39).

Quality Assessment

Studies were rated using the Downs and Blacks instrument for non-randomised studies of health care interventions[20]. Since the studies did not examine clinical effectiveness, checklist items related to comparative groups (e.g. randomisation and blinding procedures) were omitted. One reviewer (LC) scored all studies using the amended checklist and another reviewer (PM) independently scored 50% of studies drawn at random. Discrepancies between reviewers were discussed and consensus achieved.

Statistical Analysis

The systematic review extracted data at baseline, and all recorded follow-ups, for a range of different outcomes measuring disease activity, functional disability, pain, fatigue and mental well-being. Whilst traditional meta-analytical methods are used for cross-sectional data, a weighted mixed-effects model was needed to account for the aggregate level summary data of each time point over time. Multivariate meta-analyses were conducted using mixed-effects linear regression models, with a random intercept estimated to account for repeated observations within studies and a random slope for time allowing the rate of progression to vary within studies over time[21]. Since the data are aggregate level for each included cohort at each time point, they were inverse variance weighted using the study level standard error at each recorded time point. Much like a meta-analysis, this allows studies with greater sample sizes to given greater weight in the estimation of the pooled effect estimate. Full Information Maximum Likelihood (FIML) allowed for estimation of time-specific means of every cohort in the event that the data are missing. This is similar to meta-regression techniques, which assess the effect of covariates on the study level estimates. As such, the figures provided represent the estimated pooled mean for that outcome at each follow-up time-point.

Since the cohorts included will be prospective inception cohorts of patients with early RA, it was expected that the progression of all outcomes will be non-linear over time. Previous research has shown how outcomes such as functional disability follow a 'J-Shaped' trajectory in the first years of disease[22], whereby patients initially improve rapidly in the first 12-months following treatment initiation, but then worsen in the subsequent years as disease duration increases. In order to account for this non-linearity, piecewise linear splines were used with a change point at 12-months. This allows for two separate slopes to be estimated by the model, one from baseline to 12-months, and one from 12-months to 60-months. In order to quantify the data from the model, the meta-analysis will be based on the estimated pooled effect for each outcome at four pre-specified time points; baseline, 12-months, 36-months and 60-months.

For each cohort, mid-point between the first and last year of recruitment was used to place the cohorts in chronological order from earliest to latest. Cohorts were then split according to whether the recruitment was pre or post 2002. This has been used in other reviews due to its reflection of the move towards more T2T principles, and also reflects the general median year in early RA cohorts in previous reviews[23]. The dichotomised variable was entered into the mixed effect model, along with an interaction effect with follow-up time. The mean difference between pre and post -2002 cohorts will be used as the main effect estimate. These will be estimated at baseline, 12, 36 and 60-months follow-up for the Pain Visual Analogue Scale (VAS), Fatigue VAS, SF-36 PCS, SF-36 MCS, the HAQ and the DAS

outcomes. Scores <0 indicate more favourable scores for the pre-2002 cohorts, whilst scores >0 indicate more favourable scores for the post-2002 cohort. This will be expressed as both a mean difference, which highlights the change in score relative to the scale in which it was measured, as well as a Standardised Mean Difference (SMD), which allows for direct comparisons between measures with different scales. All analyse were conducted using Stata (ver15) using the 'mixed' command for mixed effects analysis.

Results

A total of 7,319 articles were identified from the 3 databases following the removal of 2,363 duplicates, as shown in Figure 1. Following title and abstract screening, 1,736 full texts were screened for eligibility. In total, 41 articles[11,22,32–41,24,42–51,25,52–61,26,62,27–31] describing data from 46 cohorts where identified, contributing a combined total of 18,046 patients. The median year of recruitment for all cohorts ranged from 1983-2014, with a median year of 2002. Cohorts recruited patients from twenty different countries (Australia[41], Austria[62], Brazil[48], Canada[24,49,53,58], Denmark[28], France[29,32,50], Germany[42,46], Iceland[54], Italy[27,31,56], Japan[35], Latin American[57], The Netherlands[25,34,36,40,59], Norway[33], Scotland[47], South Africa[51], Spain[37,61], Sweden[11,38,60], UK[22,26,39,55], USA[30,43,45,52] and Mexico[44]). The UK had the highest number of cohorts at eight (17%), followed by five (11%) from the Netherlands, and four (9%) from Canada, Sweden and the US. The characteristics of the cohorts, and the patients included in those cohorts are summarised in Table 1.

Table 1 – Summary table of cohort characteristics, and baseline summary statistics of the patients included in the cohorts.

Although contact was made with 39 authors for additional longitudinal data, only 9 responded. With respect to the data collected, 36 (78%) had measures of pain[11,22,33,35,37–40,42,44–46,24,47,49–52,54,56–59,26,61,62,27–32], 13 (28%) had measures of fatigue[26–28,39,44,46,50,52,56], nine (20%) had measures of SF-36[26,50,51,55,56,59,60], 37 (80%) had measures of the HAQ[11,22,34–41,43,44,24,45,47–52,55,56,59,25,61,62,26,28–30,32,33] and 37 (80%) had measures of DAS[11,22,33–40,42,44,24,45–47,49,50,52,53,55,56,59,26,61,62,27–32]. Alongside SF-36, other longitudinal measures of mental health were also collected, namely the Centre for Epidemiological Studies Depression Scale (CES-D)[49,53,58], The Arthritis Impact Measurement Scale (AIMS)[26] and the Hospital Anxiety and Depression Scale (HADS)[47,63], however the small numbers meant it was not possible to include them in the meta-analysis.

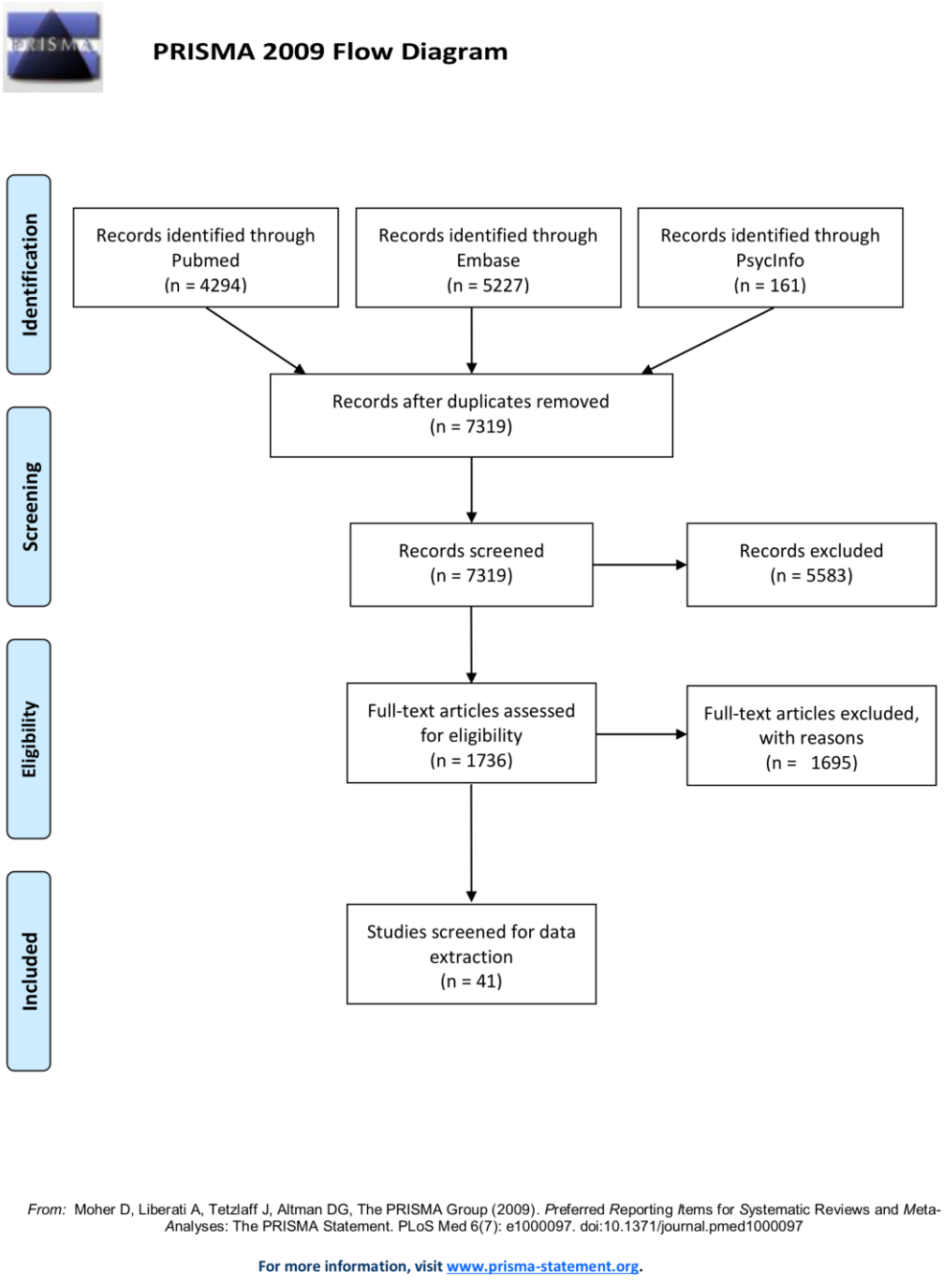

Figure 1 – Prisma Flow Diagram of journal screening process at each stage of the systematic review

Quality Assessment

A modified version of the Down's and Black Checklist was used to assess the quality of each study. Agreement between the two reviewers was high at 99%, and where there were differences, these were resolved through consultation.

Overall, all studies included in the meta-analysis were of high quality, with all studies clearly defining the hypothesis, characteristics of the patients, main findings, and estimates of variability (See supplementary material). The patients included were representative of the general population and there were no indications of 'data dredging'. However, less than 15% of the studies provided characteristics of their patients who were lost to follow-up, and only 20% of the studies appropriately accounted for this loss of follow-up in their analysis.

Whilst >80% of studies were suitably powered, described the principle confounders and appropriately accounted for the longitudinal nature of the study in their analysis, <50% of studies were found to have used appropriate statistical methods and adequately adjusted for all important confounding effects. This was largely due to the reliance on step-wise regression methods, which allow for variable selection but introduce bias in parameter estimates without regularisation[64].

Meta-Analysis

Mean Differences (MD)

The forest plots presented in Figure 2 represent the pooled (model estimated) Mean Differences (MD) between pre and post-2002 cohorts at baseline, 12, 36 and 60-months. For illustration, the sub-group pooled effect estimate for cohorts recruiting patients post-2002 for baseline Pain VAS was 52.48 (95% Confidence Intervals 48.92 to 56.05), whereas the sub-group pooled effect estimate for cohorts recruiting patients post-2002 was 48.32 (95% CI 44.51 to 52.13) (Please see Supplementary Material). This equates to a MD of -4.16 (95% CI -9.34 to 1.01), as shown in Figure 2 (allowing for rounding error).

In order to conceptualise the magnitude of the effects, the reported mean differences for each outcome were compared to changes that are deemed clinically important, often referred to as the Minimally Clinically Important Difference (MCID). Whilst thresholds vary, the MCID for pain VAS has been reported to be 11.9[65], whilst estimates for the fatigue VAS have ranged from 8.2 to 11.2 in RA populations[66]. Likewise, the MCID has been reported between 2.5 to 5.0 for the SF-36 PCS and MCS, however studies have demonstrated higher estimates of 7.1 for the SF-36 PCS[67]. As such, an estimate of 8-unit change has been illustrated in Figure 1 for the MCID for the pain, fatigue and SF-36 PCS and MCS. Likewise, a MCID of 0.20 was used for HAQ[65], and 1.00 for the DAS-28[68].

Investigation of the mean differences of all the outcomes between pre- and post-2002 studies indicate that, at baseline, pre-2002 cohorts had marginally lower levels of pain (-4.17; 95% CI -9.34 to 1.01), SF-36 MCS (-5.25; 95% CI -11.74 to 1.23) and HAQ (-0.11; 95% CI -0.27 to 0.06), whilst pre-2002 cohorts had higher levels of fatigue (3.43; 95% CI -1.32 to 8.17), SF-36 PCS (0.70; 95% CI -4.23 to 5.62) and DAS (0.18; 95% CI -0.16 to 0.51) at baseline. However, none of these differences reached statistical significance (See Figure 2).

By 12-months, all outcomes exhibit an improvement in scores. However, there is variation in the magnitude of this improvement in pre- and post-2002 cohorts for each outcome. With the SF-36 PCS there is a statistically significantly greater improvement for post-2002 cohorts relative to pre-2002 cohorts, with a MD of 7.66 (95% CI 2.57 to 12.76, $P<0.05$), and likewise for the DAS-28 and fatigue, there was a statistically significantly greater improvement for

post-2002 cohorts relative to pre-2002 cohorts, with a MD of 0.51 (95% CI 0.04 to 0.98, P<0.05) and 10.91 (95% CI 5.04 to 16.79) respectively. In contrast, whilst pain, SF-36 MCS and HAQ exhibit improvements by 12-months, the magnitude of these improvements were much smaller and did not reach statistical significance, with a MD of 3.30 (95% CI -2.67 to 9.28), 0.10 (95% CI -4.03 to 4.23) and 0.05 (95% CI -0.15 to 0.25) respectively.

Whilst pain, SF-36 MCS and the HAQ saw incremental improvements in the estimated mean differences by the 36-month and 60-month time points, these improvements were small and did not lead to any statistical differences by month 60. The SF-36 PCS remained stable over the 36 and 60-month period, with a statistically significant MD of 7.77 (95% CI 2.68 to 12.87) at month 60, whilst the post-2002 cohort continued to see greater improvements over time, with statistically significantly greater improvements by month 60 of 0.92 (95% CI 0.38 to 1.45). Only fatigue saw decreases in improvements over the 36 and 60-month period for the post-2002 cohorts, with a statistically non-significant MD of 5.74 (95% CI -1.70 to 13.18) by month 60.

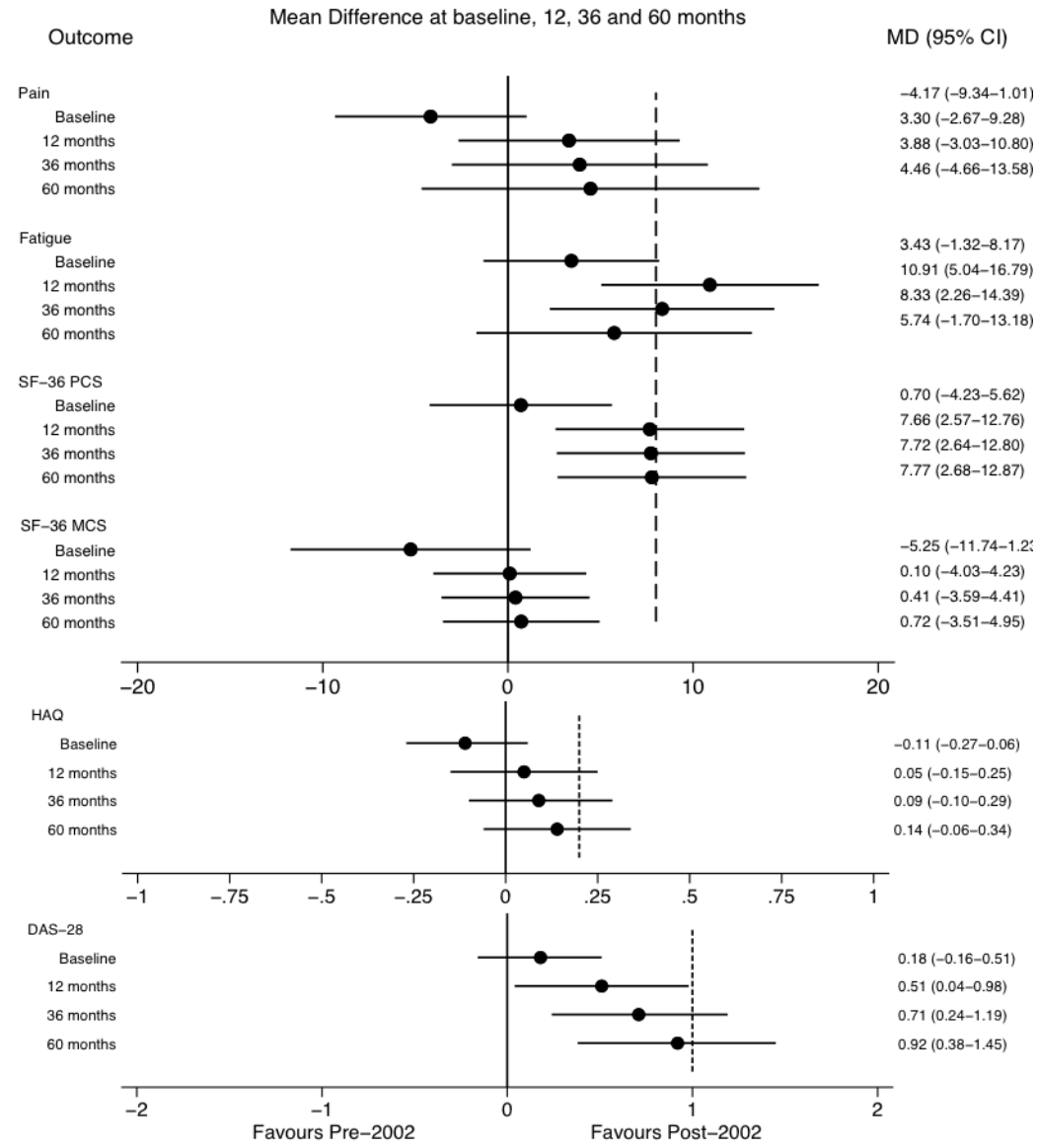

Figure 2 – Forest plot of the estimated Mean Difference (MD) for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-

36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Points that fall to the left of the zero-line indicate better outcomes in the pre-2002 cohorts, whilst those that fall to the right of the zero-line indicate better outcomes for the post-2002 cohorts. 95% Confidence Intervals are indicated by the horizontal bars on the graph and in the brackets of the text. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

This time dependent trend for pain, fatigue, SF-36, HAQ and DAS28 for both pre-2002 and post-2002 cohorts are given in Figure 3. It demonstrates the increased initial response in the first 12 months for pain, HAQ and DAS28 for both the pre and post-2002 cohorts, however the decrease in pain and HAQ is not as great as the decline in DAS28. In contrast, whilst the post-2002 cohorts saw improvements in fatigue, SF-36 PCS and SF-36 MCS in the first 12-months, the pre-2002 cohorts indicated a more stable progression over the full 60-months. By month 60, only the SF-36 PCS and DAS28 scores indicated a significant difference between the pre and post-2002 cohorts, with post-2002 cohorts indicating more favourable outcomes ($P<0.05$). However, there was no statistically significant difference between pre and post-2002 cohorts over the full 60-months for pain, SF-36 MCS and HAQ.

Sensitivity analysis

Dichotomising recruitment year into pre- and post-2002 allowed for data to be pooled into larger groups, as further stratification would have led to issues with data sparsity of outcomes over the follow-up period. However, to ensure that these groups reflected a broader linear association with recruitment year, a sensitivity analysis was conducted looking at recruitment year as a continuous outcome, rather than a binary outcome. The analysis indicated a linear association with recruitment year, with each outcome. In corroboration with the main analysis, the main of effect of recruitment year was statistically significantly associated with DAS-28, and whilst the other outcomes indicated reductions as recruitment year increased, these were smaller effects and did not reach statistical significance. A detailed report of this analysis is provided in supplementary material.

Additional analysis investigated the progression of the sub-components of the DAS28; the Swollen Joint Count (SJC), Tender Joint Count (TJC), C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR), in a sub-group of cohorts reporting this data. Of the 37 cohorts with DAS28 data, 25 had data on SJC, 23 on TJC, 22 on CRP and 18 on ESR. Whilst SJCs, TJCs and CRP showed greater declines in post-2002 compared to pre-2002 cohorts, the estimates over the follow-up periods were inconclusive due to low levels of data over the follow-up. Details of this sub-analysis are presented in the supplementary material.

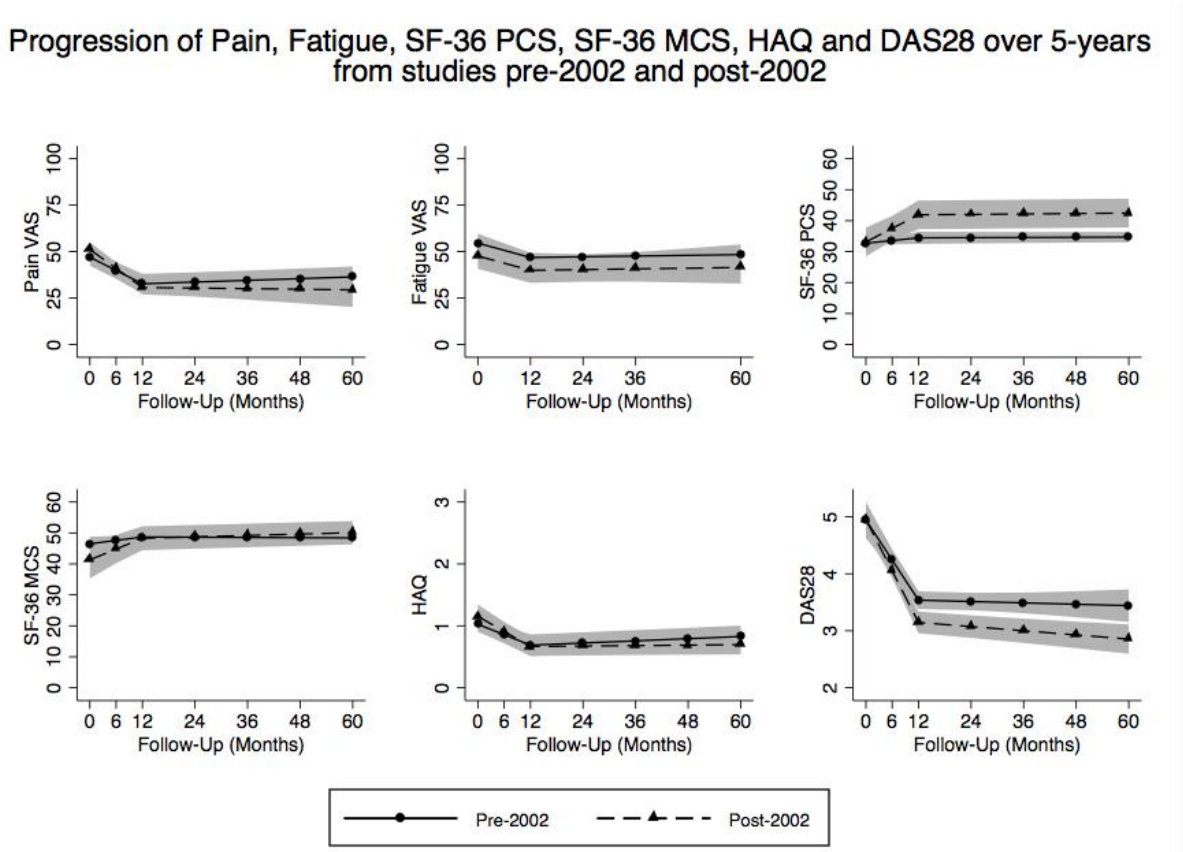

Figure 3 –Estimated marginal means for the pain, fatigue, SF-36, HAQ and DAS28 outcomes at baseline, 12, 36 and 60-month time-points. Pain, fatigue, SF-36 PCS and MCS are scored out of 100, whilst the HAQ is scored from 0 to 3 and the DAS28 from 0 to 8. Circle points with solid black lines indicate the estimated means for the pre-2002 cohorts, whilst triangle points with a dashed black line indicate the estimated means for the post-2002 cohorts. 95% Confidence Intervals are indicated by the grey shaded areas. SF-36 PCS = Short-Form 36 Physical Component Score, PCS = Short-Form 36 Mental Component Score, HAQ = Health Assessment Questionnaire, DAS28 = Disease Activity Score-28

Standardised Mean Differences (SMD)

Whilst the MD allows for differences to be examined relative to the scale in which the outcome was measured, to directly compare the magnitude of the effects of each outcome relative to each other, the MD needs to be standardised. The Standardised Mean Differences (SMD) for the DAS28 at month-60 comparing post-2002 to pre-2002 cohorts was 0.86 (95% CI 0.34 to 1.37), whilst for the SF-36 PCS it was 0.76 (95% CI 0.25 to 1.27), indicating that both demonstrated large, statistically significantly lower score for post-2002 cohorts (P<0.001).

In contrast, the SMD at month-60 comparing post-2002 to pre-2002 cohorts for pain (0.24 (95% CI -0.25 to 0.74)), fatigue (0.38 (95% CI -0.11-to 0.88)) and HAQ scores (0.34 (95% CI -0.15-to 0.84)) all indicated small to moderate effect sizes and failed to reach statistical significance in favour of post-2002 cohorts. Only the SF-36 MCS indicated improvements in favour of pre-2002 cohorts, however the effect was very small and statistically non-significant (-0.08 (95% CI -0.58 to 0.41)).

Discussion

This review is one of the first to examine the longitudinal trends of important, and well reported patient reported outcomes in inflammatory arthritis using meta-analysis. Using data from 46 early RA cohorts, with a combined total of 18,046 patients, the longitudinal meta-analysis indicated that whilst patients in more recent cohorts have large, statistically significant improvements in levels of disease activity and physical well-being over the first 60-months, pain, fatigue, physical functioning and mental well-being indicate only small, statistically non-significant improvements.

The reduction in disease activity levels is in general agreement with a previous meta-analyses that looked at longitudinal rates of structural joint damage, and found that post-2002 cohorts had statistically significantly lower joint damage than those patients recruited pre-2002[23]. Given that both reviews rely on observational cohort data, the exact cause of the decline in disease activity, and indeed other objective measures of inflammation, cannot be determined directly. However, it is likely that the move towards T2T principles of earlier, more aggressive therapies to achieve low/remission based DAS scores, along with the increased use of bDMARD therapies, are the main drivers for these secular declines[11,23,69].

Despite large effects in the reduction of disease activity, these do not translate into similar improvements in patient reported pain, functional disability and mental well-being. These findings are similar to previous meta-analyses investigating data from randomised controlled trials (RCT) for both HAQ[70], and SF-36[71] outcomes. They found that patients treated with more aggressive therapies (e.g. combination, or bDMARDs) indicated improved function and well-being, however these were not statistically significant, nor did it reflect clinically meaningful changes. These findings add more weight to the hypothesis that psychological well-being, along with functional disability, may be mediated by factors not directly influenced by inflammatory processes[10,72].

The precise role of pro-inflammatory cytokines and their association with pain and mental health is currently unclear[73]. Animal model studies have provided evidence of a link between Interleukin-1 (IL-1)[74,75], IL-6[76] and TNF-alpha[77] on depressive behaviours in mice, and cross-sectional cohort studies have shown evidence of elevated pro-inflammatory cytokines in patients with depressive symptoms[78]. However, observational studies fail to identify significant associations (both statistically and clinically) between mental health symptoms and changes in proteomic markers, such as ESR[76]. Indeed, this study also found a disconnect between fatigue and disease activity over time, suggesting that non-inflammatory processes may be involved in fatigue symptoms, such as increased levels of pain[79]. As such it is hypothesised that increased inflammation is, in part, explaining elevated symptoms in mental well-being and disability, however non-inflammatory processes also need to be considered.

Emerging research is beginning to investigate the relationship between pain and mental health could be governed by the mesolimbic dopaminergic reward system[80]. Reduced levels of dopamine have been found in patients with fibromyalgia[81,82] and there is evidence that activity in the mesolimbic reward system, specifically the role of increased dopamine neurotransmission, are strongly linked to positive emotions[83,84]. Whilst the experience of pain itself may be contributing to the reduction of dopaminergic regulation, as evidence by

reductions in patients with fibromyalgia and chronic back pain[85], the role of inflammatory makers on this system may also explain the decreased levels in RA specifically[86].

The extent to which inflammation can explain interindividual variability in mental health outcomes in all patients, or whether sub-groups of patients exist whereby inflammation plays either a lesser or more dominant role in pain experience and mental wellbeing is not yet clear. Distinct sub-groups of patients that progress differently over time has been evidenced in both functional disability[22] and disease activity measures[87], which have been demonstrated even amongst early RA patients under T2T regimes. Research by Altawil et al. has demonstrated how pain remains at high levels in a sub-group of patients, despite achieving EULAR remission, suggesting that other mechanisms of pain beyond inflammation are responsible[88]. Understanding factors associated with these different RA sub-groups, and how pain, functional disability and well-being progress over the course of the disease, would be instrumental in tailoring treatment, both pharmacological and non-pharmacological, at the early stages.

The major strengths of the study lie in its large data. The meta-analysis presented in this paper is the first, to our best knowledge, to aggregate data on numerous early RA cohorts on key clinical and patient reported outcome measures over time, with very large numbers of patients. The statistical methods used are novel in the field and allow an accurate estimation of each outcome over time, and across different periods. However, the study is not without its limitations. Large heterogeneity between studies due to the observational nature of the cohort studies included, as well as the breadth of different countries involved, makes drawing definitive conclusions on the pooled effect estimates challenging. The review includes a broad range of countries representing different GDP per capita, which has been shown in previous research to be correlated with disease activity[89]. There is some evidence to suggest socio-economic status plays an important role in the progression of functional disability and reduced quality of life[90]. However, socio-economic status is rarely reported in cohorts, making it difficult to analyse its impact in a meta-analytical setting. Additionally, every effort was made to minimise the potential bias by restricting cohorts to only early RA, as well as adopting a random-effects meta-analysis that assumes there are a range of different effects being estimated that follow an approximately normal distribution. It is reasonable to assume that country level differences in treatment prescription exist, however it is likely that most countries will have followed a similar protocol of T2T, employing broadly similar step-up treatment decisions to achieve remission/low disease. Data sparsity between the cohort periods over the follow-up for outcomes, such as fatigue, are likely to explain some of the statistically non-significant findings. Larger data samples at the later follow-up times would help narrow the intervals and provide more precision around the true effect. Publication bias is possible, but unlikely since cohort data was sought based on identification through publications that were not dependent on positive findings.

In conclusion, this longitudinal meta-analysis provides large scale data highlighting that the introduction of more aggressive, T2T based therapies coincided with improvements in disease activity and physical function over the last few decades during the first 60-months of the disease. However, these large-scale improvements in disease activity did not translate into equally large improvements in patient reported outcomes, namely pain,

functional disability and mental well-being. Whilst inflammation remains a key target, these findings provide clear support for rheumatologists to go beyond the consideration of just the DAS in their T2T approach. Non-pharmacological treatments, for managing pain, improving functional disability and improving psychological well-being are available and need to be more widely adopted in routine care.

References

1. Alamanos, Y. & Drosos, A. A. Epidemiology of adult rheumatoid arthritis. *Autoimmun. Rev.* **4**, 130–6 (2005).
2. National Institute for Clinical Excellence. *Rheumatoid arthritis*. (2990).
3. Grigor, C. *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* **364**, 263–269 (2004).
4. Smolen, J. S. *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann. Rheum. Dis.* **69**, 964–975 (2010).
5. Nikiphorou, E. *et al.* Secular Changes in Clinical Features at Presentation of Rheumatoid Arthritis: Increase in Comorbidity But Improved Inflammatory States. *Arthritis Care Res.* **69**, (2017).
6. Carpenter, L. *et al.* Reductions in radiographic progression in early RA over 25-years: Changing contribution from RF in 2 multi-centre UK inception cohorts. *Arthritis Care Res. (Hoboken).* (2017).
7. Schipper, L. G. *et al.* A tight control treatment strategy aiming for remission in early rheumatoid arthritis is more effective than usual care treatment in daily clinical practice: a study of two cohorts in the Dutch Rheumatoid Arthritis Monitoring registry. *Ann. Rheum. Dis.* **71**, 845–50 (2012).
8. Walsh, D. A. & McWilliams, D. F. Pain in rheumatoid arthritis. *Curr. Pain Headache Rep.* **16**, 509–517 (2012).
9. van Steenbergen, H. W., Tsonaka, R., Huizinga, T. W. J., Boonen, A. & van der Helm-van Mil, A. H. M. Fatigue in rheumatoid arthritis; a persistent problem: a large longitudinal study. *RMD Open* **1**, e000041–e000041 (2015).
10. Overman, C. L. *et al.* Change of Psychological Distress and Physical Disability in Patients With Rheumatoid Arthritis Over the Last Two Decades. *Arthritis Care Res. (Hoboken).* **66**, 671–678 (2014).
11. Ahlstrand, I., Thyberg, I., Falkmer, T., Dahlström & Björk, M. Pain and activity limitations in women and men with contemporary treated early RA compared to 10 years ago: The Swedish TIRA project. *Scand. J. Rheumatol.* **44**, 259–264 (2015).
12. Dickens, C., McGowan, L., Clark-Carter, D. & Creed, F. Depression in rheumatoid arthritis: a systematic review of the literature with meta-analysis. *Psychosom. Med.* **64**, 52–60 (2002).
13. Pincus, T., Griffith, J., Pearce, S. & Isenberg, D. Prevalence of self-reported depression in patients with rheumatoid arthritis. *Br. J. Rheumatol.* **35**, 879–83 (1996).
14. Matcham, F. *et al.* The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis. *Semin. Arthritis Rheum.* **44**, 123–130 (2014).
15. Isik, A., Koca, S. S., Ozturk, A. & Mermi, O. Anxiety and depression in patients with rheumatoid arthritis. *Clin. Rheumatol.* **26**, 872–878 (2007).

16. Hider, S. L., Tanveer, W., Brownfield, A., Mattey, D. L. & Packham, J. C. Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic. *Rheumatology* **48**, 1152–1154 (2009).
17. Ethgen, O., Kahler, K. H., Kong, S. X., Reginster, J.-Y. & Wolfe, F. The effect of health related quality of life on reported use of health care resources in patients with osteoarthritis and rheumatoid arthritis: a longitudinal analysis. *J. Rheumatol.* **29**, 1147–55 (2002).
18. Jakobsson, U. & Hallberg, I. R. Pain and quality of life among older people with rheumatoid arthritis and/or osteoarthritis: a literature review. *J. Clin. Nurs.* **11**, 430–43 (2002).
19. Carpenter, L. *et al.* Validation of methods for converting the original Disease Activity Score (DAS) to the DAS28. *Rheumatol. Int.* 1–9 (2018).
20. Downs, S. H. & Black, N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J. Epidemiol. Community Heal.* **52**, 377–384 (1998).
21. Ishak, K. J., Platt, R. W., Joseph, L., Hanley, J. A. & Caro, J. J. Meta-analysis of longitudinal studies. *Clin. Trials J. Soc. Clin. Trials* **4**, 525–539 (2007).
22. Norton, S. *et al.* Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. *Rheumatology (Oxford).* **52**, 2016–24 (2013).
23. Carpenter, L. *et al.* Have radiographic progression rates in early rheumatoid arthritis changed? A systematic review and meta-analysis of long-term cohorts. *Rheumatol. (United Kingdom)* **55**, (2016).
24. Barnabe, C. *et al.* Heterogeneous Disease Trajectories Explain Variable Radiographic, Function and Quality of Life Outcomes in the Canadian Early Arthritis Cohort (CATCH). *PLoS One* **10**, e0135327 (2015).
25. Ajeganova, S. *et al.* Disease-modifying antirheumatic drug-free sustained remission in rheumatoid arthritis: An increasingly achievable outcome with subsidence of disease symptoms. *Ann. Rheum. Dis.* **75**, 867–873 (2016).
26. Gwinnutt, J. M. *et al.* Twenty-Year Outcome and Association Between Early Treatment and Mortality and Disability in an Inception Cohort of Patients With Rheumatoid Arthritis: Results From the Norfolk Arthritis Register. *Arthritis Rheumatol.* **69**, 1566–1575 (2017).
27. Cantini, F., Niccoli, L., Cassarà, E., Kaloudi, O. & Nannini, C. Sustained maintenance of clinical remission after adalimumab dose reduction in patients with early psoriatic arthritis: A long-term follow-up study. *Biol. Targets Ther.* **6**, 201–206 (2012).
28. Christensen, A. W. *et al.* Ultrasound Doppler but not temporal summation of pain predicts DAS28 response in rheumatoid arthritis: A prospective cohort study. *Rheumatol. (United Kingdom)* **55**, 1091–1098 (2016).
29. Combe, B. *et al.* Predictive factors of 5-year health assessment questionnaire disability in early rheumatoid arthritis. *J Rheumatol* **30**, 2344–2349 (2003).
30. Craig, S. M. *et al.* Vitamin D status and its associations with disease activity and severity in african americans with recent-onset rheumatoid arthritis. *J. Rheumatol.* **37**, 275–281 (2010).
31. Di Franco, M. *et al.* Hypovitaminosis D in recent onset rheumatoid arthritis is predictive of reduced response to treatment and increased disease activity: a 12 month follow-up study. *BMC Musculoskelet. Disord.* **16**, 53 (2015).
32. Flipon, E. *et al.* Is it possible to identify early predictors of the future cost of chronic

arthritis? the VErA project. *Fundam. Clin. Pharmacol.* **23**, 105–113 (2009).
33. Haugeberg, G., Bøyesen, P., Helgetveit, K. & Prøven, A. Clinical and Radiographic Outcomes in Patients Diagnosed with Early Rheumatoid Arthritis in the First Years of the Biologic Treatment Era: A 10-year Prospective Observational Study. *J. Rheumatol.* **42**, 2279–87 (2015).
34. Jansen L.M.A., Van Schaardenburg D., Van Der Horst-Bruinsma I.E., Bezemer P.D., D. B. A. C. Predictors of functional status in patients with early rheumatoid arthritis. *Ann. Rheum. Dis.* **59**, 223–226 (2000).
35. Kaneko, Y., Kuwana, M., Kondo, H. & Takeuchi, T. Discordance in global assessments between patient and estimator in patients with newly diagnosed rheumatoid arthritis: Associations with progressive joint destruction and functional impairment. *J. Rheumatol.* **41**, 1061–1066 (2014).
36. Kievit, W. *et al.* Comment on the use of self-reporting instruments to assess patients with rheumatoid arthritis: The longitudinal association between the DAS28 and the VAS general health. *Arthritis Care Res.* **55**, 745–750 (2006).
37. Sanmarti, R. *et al.* Radiological progression in early rheumatoid arthritis after DMARDS: A one-year follow-up study in a clinical setting. *Rheumatology* **42**, 1044–1049 (2003).
38. Svensson, B. *et al.* Persistently active disease is common in patients with rheumatoid arthritis, particularly in women: a long-term inception cohort study. *Scand. J. Rheumatol.* **45**, 448–455 (2016).
39. Twigg, S. *et al.* Fatigue, older age, higher body mass index and female gender predict worse disability in early rheumatoid arthritis despite treatment to target: A comparison of two observational cohort studies from the United Kingdom. *Arthritis Care Res. (Hoboken).* (2017).
40. Van Der Leeden, M. *et al.* Prediction of walking disability by disease-related factors in patients with rheumatoid arthritis. *J. Rehabil. Med.* **42**, 506–510 (2010).
41. Wechalekar, M. D. *et al.* Active Foot Synovitis in Patients With Rheumatoid Arthritis: Unstable Remission Status, Radiographic Progression, and Worse Functional Outcomes in Patients With Foot Synovitis in Apparent Remission. *Arthritis Care Res.* **68**, 1616–1623 (2016).
42. Westhoff, G., Buttgereit, F., Gromnica-ihle, E. & Zink, A. Morning stiffness and its influence on early retirement in patients with recent onset rheumatoid arthritis. *Rheumatology* **47**, 980–984 (2008).
43. Wolfe, F. & Sharp, J. T. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* **41**, 1571–1582 (1998).
44. Amjadi, S. S. *et al.* Validating and assessing the sensitivity of the Health Assessment Questionnaire-Disability Index-derived Short Form-6D in patients with early aggressive rheumatoid arthritis. *J Rheumatol* **36**, 1150–1157 (2009).
45. Paulus, H. E., Bulpitt, K. J., Ramos, B., Park, G. & Wong, W. K. Relative contributions of the components of the American College of Rheumatology 20% criteria for improvement to responder status in patients with early seropositive rheumatoid arthritis. *Arthritis Rheum.* **43**, 2743–2750 (2000).
46. Callhoff, J., Albrecht, K., Schett, G., Zink, A. & Westhoff, G. Depression is a stronger predictor of the risk to consider work disability in early arthritis than disease activity or response to therapy. *RMD Open* **1**, 1–6 (2015).
47. Dale, J. *et al.* The Scottish Early Rheumatoid Arthritis (SERA) Study: an inception

cohort and biobank. *BMC Musculoskelet. Disord.* **17**, 1–8 (2016).
48. da Mota, L. M. *et al.* Baseline HAQ and SF-36 questionnaire scores cannot predict clinical remission, radiographic progression or the need for biological therapy in a three-year prospective study of a Brazilian early rheumatoid arthritis cohort. *Rheumatol Int* **32**, 3937–3943 (2012).
49. Dobkin, P. L. *et al.* Predictors of Pain for Patients With Early Inflammatory Polyarthritis. *Arthritis Care Res. (Hoboken).* **65**, 992–999 (2013).
50. Che, H. *et al.* Performance of patient reported outcomes in the assessment of rheumatoid arthritis disease activity: The experience of the ESPOIR cohort Disease activity by patient reported outcomes. 1–29 (2014).
51. Hodkinson, B. *et al.* Functional disability and health-related quality of life in South Africans with early rheumatoid arthritis. *Scand. J. Rheumatol.* **41**, 366–374 (2012).
52. Jawaheer, D. *et al.* Disease progression and treatment responses in a prospective DMARD-naive seropositive early rheumatoid arthritis cohort: does gender matter? *J Rheumatol* **37**, 2475–2485 (2010).
53. Leblanc-Trudeau, C. *et al.* Depressive symptoms predict future simple disease activity index scores and simple disease activity index remission in a prospective cohort of patients with early inflammatory polyarthritis. *Rheumatology (Oxford).* **54**, 2205 (2015).
54. Manfredsdottir, V. F. *et al.* The effects of tobacco smoking and rheumatoid factor seropositivity on disease activity and joint damage in early rheumatoid arthritis. *Rheumatology* **45**, 734–740 (2006).
55. McWilliams, D. F., Kiely, P. D. W., Young, A. & Walsh, D. A. Baseline factors predicting change from the initial DMARD treatment during the first 2 years of rheumatoid arthritis: Experience in the ERAN inception cohort. *BMC Musculoskelet. Disord.* **14**, 7–10 (2013).
56. Picchianti-Diamanti, A. *et al.* Health-related quality of life and disability in patients with rheumatoid, early rheumatoid and early psoriatic arthritis treated with etanercept. *Qual. Life Res.* **19**, 821–826 (2010).
57. Ramagli, A. *et al.* Characteristics of patients with early-onset arthritis in Latin America: Description of the REPANARC cohort. *J. Clin. Rheumatol.* **21**, 283–288 (2015).
58. Schieir, O. *et al.* Symptoms of Depression Predict the Trajectory of Pain Among Patients with Early Inflammatory Arthritis: A Path Analysis Approach to Assessing Change. *J. Rheumatol.* **36**, 231–239 (2009).
59. Steunebrink, L. M. M. *et al.* Recently diagnosed rheumatoid arthritis patients benefit from a treat-to-target strategy: results from the DREAM registry. *Clin. Rheumatol.* **35**, 609–615 (2016).
60. West, E. & Wållberg-Jonsson, S. Health-related quality of life in Swedish men and women with early rheumatoid arthritis. *Gend. Med.* **6**, 544–554 (2009).
61. Villaverde García, V. *et al.* [What are patients with early rheumatoid arthritis like in Spain? Description of the PROAR cohort]. *Reumatol. Clin.* **5**, 115–20 (2009).
62. Machold, K. P. *et al.* Very recent onset rheumatoid arthritis: clinical and serological patient characteristics associated with radiographic progression over the first years of disease. *Rheumatol.* **46**, 342–349 (2007).
63. Norton, S. *et al.* Trajectories of functional limitation in early rheumatoid arthritis and their association with mortality. *Rheumatol. (United Kingdom)* **52**, 2016–2024 (2013).

64. Steyerberg, E. W., Eijkemans, M. J. C. & Habbema, J. D. F. Stepwise Selection in Small Data Sets: A Simulation Study of Bias in Logistic Regression Analysis. *J. Clin. Epidemiol.* **52**, 935–942 (1999).
65. Pope, J. E., Khanna, D., Norrie, D. & Ouimet, J. M. The Minimally Important Difference for the Health Assessment Questionnaire in Rheumatoid Arthritis Clinical Practice Is Smaller Than in Randomized Controlled Trials. *J. Rheumatol.* **36**, 254–259 (2009).
66. Khanna, D. *et al.* The minimally important difference for the fatigue visual analog scale in patients with rheumatoid arthritis followed in an academic clinical practice. *J. Rheumatol.* **35**, 2339–43 (2008).
67. Ward, M. M., Guthrie, L. C. & Alba, M. I. Clinically important changes in short form 36 health survey scales for use in rheumatoid arthritis clinical trials: the impact of low responsiveness. *Arthritis Care Res. (Hoboken).* **66**, 1783–9 (2014).
68. Ward, M. M., Guthrie, L. C. & Alba, M. I. Clinically important changes in individual and composite measures of rheumatoid arthritis activity: thresholds applicable in clinical trials. *Ann. Rheum. Dis.* **74**, 1691–6 (2015).
69. Finckh, A., Choi, H. K. & Wolfe, F. Progression of radiographic joint damage in different eras: trends towards milder disease in rheumatoid arthritis are attributable to improved treatment. *Ann. Rheum. Dis.* **65**, 1192–1197 (2006).
70. Barra, L., Ha, A., Sun, L., Fonseca, C. & Pope, J. Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons. *Clin. Exp. Rheumatol.* **32**, 333–41
71. Matcham, F. *et al.* The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register. *Rheumatology* **57**, 835–843 (2018).
72. Andersson, M. L. E., Forslind, K., Hafström, I. & BARFOT Study Group. Patients with Early Rheumatoid Arthritis in the 2000s Have Equal Disability and Pain Despite Less Disease Activity Compared with the 1990s: Data from the BARFOT Study over 8 Years. *J. Rheumatol.* **44**, 723–731 (2017).
73. Nerurkar, L., Siebert, S., Mcinnes, I. B. & Cavanagh, J. Review Rheumatoid arthritis and depression: an inflammatory perspective. *The Lancet Psychiatry* (2018).
74. Bluthé, R. M. *et al.* Synergy between tumor necrosis factor alpha and interleukin-1 in the induction of sickness behavior in mice. *Psychoneuroendocrinology* **19**, 197–207 (1994).
75. Owen, B. M., Eccleston, D., Ferrier, I. N. & Young, A. H. Raised levels of plasma interleukin-1beta in major and postviral depression. *Acta Psychiatr. Scand.* **103**, 226–8 (2001).
76. Choy, E. H. S. & Calabrese, L. H. Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis. *Rheumatology (Oxford).* **57**, 1885–1895 (2018).
77. Tuglu, C., Kara, S. H., Caliyurt, O., Vardar, E. & Abay, E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl).* **170**, 429–433 (2003).
78. Kojima, M. *et al.* Depression, inflammation, and pain in patients with rheumatoid arthritis. *Arthritis Rheum.* **61**, 1018–1024 (2009).
79. Castrejon, I. *et al.* Assessment of fatigue in routine care on a Multidimensional Health Assessment Questionnaire (MDHAQ): a cross-sectional study of associations with RAPID3 and other variables in different rheumatic diseases. *Clin. Exp. Rheumatol.* **34**,

901–909
80. Sturgeon, J. A., Finan, P. H. & Zautra, A. J. Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat. Rev. Rheumatol.* **12**, 532–542 (2016).
81. Wood, P. B., Glabus, M. F., Simpson, R. & Patterson, J. C. Changes in Gray Matter Density in Fibromyalgia: Correlation With Dopamine Metabolism. *J. Pain* **10**, 609–618 (2009).
82. Wood, P. B. *et al.* Fibromyalgia patients show an abnormal dopamine response to pain. *Eur. J. Neurosci.* **25**, 3576–3582 (2007).
83. Schultz, W. Getting formal with dopamine and reward. *Neuron* **36**, 241–63 (2002).
84. Ashby, F. G., Isen, A. M. & Turken, A. U. A neuropsychological theory of positive affect and its influence on cognition. *Psychol. Rev.* **106**, 529–50 (1999).
85. Baliki, M. N., Geha, P. Y., Fields, H. L. & Apkarian, A. V. Predicting Value of Pain and Analgesia: Nucleus Accumbens Response to Noxious Stimuli Changes in the Presence of Chronic Pain. *Neuron* **66**, 149–160 (2010).
86. Miller, A. H., Haroon, E., Raison, C. L. & Felger, J. C. Cytokine targets in the brain: Impact on neurotransmitters and neurocircuits. *Depress. Anxiety* **30**, 297–306 (2013).
87. Siemons, L., ten Klooster, P. M., Vonkeman, H. E., Glas, C. A. W. & van de Laar, M. A. F. J. Distinct Trajectories of Disease Activity Over the First Year in Early Rheumatoid Arthritis Patients Following a Treat-to-Target Strategy. *Arthritis Care Res. (Hoboken).* **66**, 625–630 (2014).
88. Altawil, R. *et al.* Remaining Pain in Early Rheumatoid Arthritis Patients Treated With Methotrexate. **68**, 1061–1068 (2016).
89. Sokka, T. *et al.* Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. *Ann. Rheum. Dis.* **68**, 1666–1672 (2009).
90. Verstappen, S. M. M. The impact of socio-economic status in rheumatoid arthritis. *Rheumatology* **56**, kew428 (2016).

Author	Year Published	Cohort	Country	Year Recruited		Followup (Months)	N	Baseline Pain* (Mean (SD))		Baseline Fatigue* (Mean (SD))		Baseline SF36 PCS (Mean (SD))		Baseline SF36 MCS (Mean (SD))		Baseline HAQ (Mean (SD))		Baseline DAS (Mean (SD))		Age	Female (%)	RF + (%)
Ahlstrand et al.	2015	TIRA-1	Sweden	1996	1998	36	276	48.10	(25)							0.90	(0.6)	5.20	(1.2)	56	69	
Ahlstrand et al.	2015	TIRA-2	Sweden	2006	2009	36	373	52.60	(24)							1.00	(0.6)	5.10	(1.3)	59	67	
Ajeganova et al.	2016	Leiden	Netherlands	1993	2011	120	886									1.00	(0.87)			57	67	59
Amjadi et al.	2009	Mexico/US cohort	USA/Mexico	1993	2009	12	277	58.90	(28)	52.60	(24.3)					1.20	(0.7)	6.00	(1.1)	51	77	
Barnabe et al.	2015	CATCH	Canada	2007	2014	24	1586	55.00	(2.9)							1.03	(0.71)	5.06	(1.45)	54	73	66
Callhoff et al.	2015	CAPEA cohort	Germany	2010	2013	24	512	54.20	(2.6)	39.00	(2.86)							4.40	(1.4)	47	68	57
Cantini et al.	2012	Prato Cohort RA	Italy	2008	2010	36	55	69.00	(11)	62.00	(14.9)							5.48	(0.34)	50	40	89
Che et al.	2014	ESPOIR Cohort	France	2002	2005	60	664	39.60	(28)	48.90	(27.4)	37.90	(8.4)	39.30	(10.8)	1.03	(0.69)	5.30	(1.2)	49	77	46
Christensen et al.	2016	Copenhagen Cohort	Denmark	2013	2014	4	102	49.94	(24)	56.28	(26.9)					1.05	(0.65)	4.48	(1.1)	55	75	64
Combe et al.	2003	French Cohorts	France	1993	1994	60	140	57.50	(22)							1.30	(0.7)	4.10	(0.8)	51	73	81
Craig et al.	2010	CLEAR	USA	2000	2010	36	266	61.00	(2.9)							1.59	(0.92)	3.90	(1.5)	51	81	69
Da Mota et al.	2012	Brazil Cohort	Brazil	2012	2012	36	40									1.89	(0.78)			45	90	
Dale et al.	2016	SERA	Scotland	2011	2015	24	1073	51.96	(28)							1.17	(0.79)	4.74	(1.34)	58	65	72
Di Franco et al.	2015	Rome Cohort	Italy	2010	2012	12	37	63.00	(24)									5.18	(1)	47	84	83
Dobkin et al.	2013	CHUS Cohort	Canada	2006	2011	12	211	48.90	(27)							0.79	(0.61)	4.80	(1.4)	59	63	33
Flipon et al.	2009	VeRA	France	1998	2001	0	180	42.90	(26)							1.00	(0.72)	3.22	(1.3)	56	71	
Garcia et al.	2009	PROAR	Spain	2001	2005	60	171	55.21	(24)							1.40	(0.71)	5.80	(1.19)	54	70	52
Gwinnutt et al.	2017	NOAR-Cohort 1	UK	1990	1994	120	608									1.09	(0.737)	4.69	(1.19)	55	66	52
Gwinnutt et al.	2017	NOAR-Cohort 2	UK	1995	1999	84	453									1.13	(0.761)	4.48	(1.22)	57	69	59
Gwinnutt et al.	2017	NOAR-Cohort 3	UK	2000	2004	120	340	45.38	(26)	49.31	(27.2)	31.71	(9.89)	45.94	(11.9)	1.23	(0.765)	4.25	(1.12)	58	69	69
Gwinnutt et al.	2017	NOAR-Cohort 4	UK	2005	2008	120	304	46.84	(26)	50.78	(28.5)					1.18	(0.702)	4.42	(1.18)	55	69	74
Haugeberg et al.	2015	Norway Cohort	Norway	1999	2001	120	94	44.20	(25)							0.69	(0.51)	5.20	(1.1)	50	62	68
Hodkinson et al.	2012	GREAT Registry	South Africa	2005	2008	12	171	66.10	(25)			34.20	(16.9)	44.90	(18.5)	1.67	(0.79)			47	82	85
Jansen et al.	2000	Amsterdam Cohort	Netherlands	1995	1996	12	133									1.10	(0.8)	5.40	(1.2)	64	68	50
Jawaheer et al.	2010	West US & Mexico Cohort	USA	1993	2002	24	292	60.40	(27)	52.00	(24.6)					1.20	(0.7)	5.10	(1.1)	50	75	72
Kaneko et al.	2014	SAKURA Cohort	Japan	2007	2009	12	75	43.90	(29)							0.76	(0.713)	4.52	(1.15)	61	86	79
Kievit et al.	2006	UMCN/SMK	Netherlands	1985	2004	36	908									0.77	(0.6)	5.20	(1.3)	54	66	77
Leblanc-Trudeau et al.	2015	EUPA	Canada	1998	2013	42	275											4.80	(1.9)	60	63	36
Machold et al.	2007	AEAA	Austria	1996	2001	36	55	48.60	(22)							0.91	(0.89)	5.60	(1)	52	76	44

Manfredsdottir et al.	2006	Reykjavik Cohort	Iceland	1997	2000	24	100	63.00	(2.5)											53	57	47
McWilliams et al.	2013	ERAN	UK	2002	2011	60	997					29.12	(12.1)	47.30	(11.7)	1.08	(0.76)	4.68	(1.56)	57	68	53
Norton et al.	2013	ERAS	UK	1986	2001	120	1465	43.97	(26)							1.15	(0.769)	4.77	(1.26)	55	66	73
Paulus et al.	2000	US Western Consortium Cohort	USA	1993	1996	24	180	60.10	(27)							1.22	(0.73)	4.92	(1.14)	52	78	
Picchianti-Diamanti et al.	2010	Rome RA Cohort	Italy	2005	2006	24	20	58.50	(24)	77.70	(11.8)	25.60	(3.9)	29.50	(9)	1.16	(0.6)	4.90	(1.1)	53	75	
Ramagli et al.	2015	REPANARC Cohort	Latin America	2010	2013	24	173	60.00	(2.7)											42	84	47
Sanmarti et al.	2003	Barcalona Cohort	Spain	1998	2000	12	60	51.20	(22)							1.00	(0.5)	5.80	(0.8)	52	78	78
Schieir et al.	2009	McEar	Canada	2004	2007	6	320	80.00	(8.6)											57	69	
Steunebrink et al.	2016	DREAM Registry	Netherlands	2012	2015	12	91	58.40	(22)			37.30	(9.2)	44.80	(11.8)	0.90	(0.7)	4.90	(1.2)	59	60	58
Svensson et al.	2016	BARFOT	Sweden	1993	1999	96	640	45.00	(24)							1.00	(0.6)	5.10	(1.2)	54	66	60
Twigg et al.	2017	IACON	UK	2010	2014	24	384	46.00	(2.8)	44.00	(2.9)					1.12	(0.73)	3.94	(1.4)	56	70	57
Twigg et al.	2017	YEAR	UK	2002	2009	24	725	58.00	(2.6)	45.00	(2.6)					1.27	(0.75)	4.70	(1.5)	58	67	70
van der Leeden et al.	2010	EAC	Netherlands	1995	2007	96	845	50.82	(25)							1.21	(0.76)	5.20	(1.2)	55	69	51
Wechalekar et al.	2016	Adelaide EAC Cohort	Australia	2000	2014	36	263									0.76	(0.55)			55	71	60
West et al.	2009	Umea Cohort	Sweden	1996	1998	72	50					33.10	(11.5)	48.40	(10.1)					51	68	92
Westhoff et al.	2008	German Cohort	Germany	2000	2001	36	916	43.00	(2.6)									4.79	(1.5)	57	70	
Wolfe et al.	1998	Withita Cohort	USA	1973	1993	228	256									0.89	(0.7)			52	73	74

*Where studies reported the Visual Analogue Scale from 0-10, they were converted to 0-100.